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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/005,073 | 12/07/2001 | Anthony M. Jevnikar | 024916-011 | 8806 |

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| EXAMINER | |
|---|---|
| EWOLDT, GERALD R | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/005,073 | JEVNIKAR ET AL. | |
| | Examiner | Art Unit | |
| | G. R. Ewoldt, Ph.D. | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *52-101* is/are pending in the application.

4a) Of the above claim(s) *53-58,62,64-68,92-94 and 96-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52,59-61,63,69-91 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**DETAILED ACTION**

1. Applicant's remarks filed 10/18/05 are acknowledged.

2. Claims 53-58, 62, 64-68, 92-94, and 96-101 stand withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to nonelected species.

Claims 52, 59-61, 63, 69-91, and 95 are being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 52, 59-61, 63, 69-91, and 95 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record set forth in the action mailed 2/10/04 and maintained in the actions mailed 10/08/04 and 4/18/05.

As set forth in the last action, Applicant's arguments, filed 2/08/05, have been fully considered but they are not persuasive. Applicant's remarks highlight the points and arguments of the instant declaration of Inventor Jevnikar. Accordingly, the declaration is addressed here.

The Inventor begins by discounting the teachings of the 1999 Marketletter Newsletter because the newspaper publication is not peer reviewed and may contain errors.

It is noted that Applicant has not actually addressed the substance of the document, i.e., that compositions that were successful in inducing tolerance in animal models were not successful in humans. This teaching alone clearly establishes the unpredictability of the claimed methods and compositions.

The Inventor argues that the reference to unpredictability in the Goodnow (2001) paper refers to the use and mechanism of action of corticosteroids.

Applicant is simply incorrect, or at best incomplete, in his description of the Goodnow reference. The unpredictability also refers to methods of "chronically stimulating antigen receptors with antigen or antibodies to the receptor", i.e., methods of inducing tolerance.

The Inventor argues that the teachings of WO 02/053092 do not involve oral administration of plant materials, but the reference does show that immune tolerance can be accomplished.

It is the Examiner's position that the reference teaches what it teaches - the induction of oral tolerance is fraught with numerous obstacles not addressed in the instant application. Also note that the Inventor has not addressed the teaching of the reference that the induction of oral tolerance requires "extensive empirical experimentation". Additionally, it must be noted that even though the Inventor discounted the factual teachings of the Marketletter document (i.e., that oral tolerance trials were stopped) because it was not peer reviewed, the Inventor here accepts certain teachings that might support the inventions of the instant claims, even though the teachings of a WO document also are not peer reviewed.

The Inventor states, "I further disagree with the Examiner's statement that oral tolerance has never before been successfully demonstrated in humans".

What the Examiner actually wrote in the previous action was:
"Whereas tolerance has been repeatedly induced in mice, the identical/equivalent methods have not worked in humans".

The Inventor has submitted two references, Husby et al. (1994) and McKown et al. (2000), assertedly teaching the induction of tolerance in humans.

Regarding the Husby et al. reference, the reference teaches the reduction of *in vitro* T cell proliferation and delayed skin test responses to KLH. The reference further teaches that no reduction in B cell responses was observed. The authors speculate that it was only a Th1 response that was reduced. Clearly then, the reference cannot enable the broad methods and compositions of the instant claims that recite the suppressing or reducing of *any* type of immune response. Interestingly, the authors point to the clinical studies of Weiner et al. to address the question of whether or not the feeding of antigens can be used to treat MS or RA. It is those very studies that were reported as being stopped in the *Marketletter* reference.

Upon further review of the work of the scientific group of which Husby was a member, Elson et al., it was found that the group reported in 2004 (Moldoveanu et al.) the failure of oral tolerance in suppressing an ongoing immune response. Using the same KLH antigen model as used some ten years earlier in Husby et al., the reference states "some form of immunomodulation greater than that provided by the oral administration of antigen alone is required in humans for suppression of an existing immune response". This would appear to be a direct teaching that the inventions of the instant claims cannot work as broadly claimed.

Regarding the McKown et al reference., the reference provides encouraging preliminary data indicating that oral administration of type I collagen (CI) might be useful for treating systemic sclerosis (SSc). Note that regarding tolerance, however, the reference teaches only that IFNγ production was reduced which, "suggests that oral tolerance to CI was effected". Note another teaching of the reference, specifically, an unexplainable reduction in IL-10 (which was previously reported to be *upregulated* in other models of oral tolerance). Also note the conclusions of the reference, i.e., "Further evaluation of oral tolerance to CI in patients with SSc is justified," and "Oral CI administration appears to be safe. Its efficacy needs to be assessed by a larger placebo-controlled, double-blind trial". It appears then that even this specific embodiment of the induction of oral tolerance has not risen past the level of idea. Thus, it cannot support the broad inventions of the instant claims.

Upon further review the work of the scientific group including McKown et al., numerous examples in which no sign of oral tolerance induction could be induced can be found. See for example, McKown et al. (1999), in which the authors document the lack of efficacy of the oral administration of type II collagen for the treatment of RA.

More interestingly, see Carbone et al. (2004) in which, in this instance, the oral administration of CI had no effect on SSc patients. Given the same group's report of encouraging results with the same composition in the same patients four years earlier in the McKown et al. (2000) reference, it would appear that the group was simply employing methods of trial-and-error (unsuccessfully) in their attempts to induce tolerance in SSc patients. As methods of trial-and-error provide no particular expectation of success with any particular embodiment (as aptly demonstrated here), said methods are considered to be inherently unpredictable and requiring of undue experimentation. Further note that this *demonstration* of unpredictability in 2004 must call into question the enablement of the methods and compositions of the instant claims that claim priority to 1993.

The Inventor asserts that the unpublished results of an NIH trial demonstrate that oral tolerance can be induced in humans.

The Examiner cannot evaluate or comment on data that has not been submitted for review.

The Inventor argues that the use of the term "unexpected" in a previous declaration was not an admission of the unexpected nature of the instant invention.

It is presumed that the previous declaration was prepared and reviewed with the assistance of representatives skilled in patent prosecution, i.e., Applicant is not *pro se*. Accordingly, Applicant's choice of the terms "not predictable" in section 12 and "unexpected" in section 14 must be considered to be intentional and the terms must be considered to have their normal meanings when used in the patent prosecution context.

The Inventor asserts, "In the case of both mice and humans, immune responses in lymphocytes upon *in vitro* challenge to a specific protein is similarly attenuated or changed following oral administration of the protein. No qualitative or quantitative differences are found in the pattern of cytokines released or T cell activity and so mice and humans share a common biological response to oral protein antigens".

The Inventor's unsupported assertions aside, the facts of record clearly demonstrate that the induction of tolerance in humans is at best highly unpredictable. Even in the few documented instances wherein some degree of T cell tolerance may have been established, e.g., Husby et al. (1994), said possible tolerance appears to have been the result of random chance or simple trial-and-error, given the documented failures of the same groups, e.g., Moldoveanu et al. (2004). The Examiner cannot simply ignore the failure upon failure in establishing efficacious tolerance in humans set forth in the prior art. And it must be noted that the methods and compositions of the instant claims recite essentially *no* limitations as regard the diseases to be treated or the antigens to be used. Further note that the specification provides *no* guidance regarding the parameters of tolerance induction, e.g., dosages to be used or the timing of administration. Finally, assuming *arguendo*, that tolerance in humans has been demonstrated, e.g., the unpublished NIH study set forth in the Inventor's declaration, it is unclear how results still unpublished in 2005 could enable the instant claims as of their priority date of 1993.

Applicant's arguments, filed 10/18/05, have been fully considered but they are not persuasive. Applicant attempts to discount the teachings of the *Marketletter* as did the Inventor previously, e.g., it lacks credibility and is not peer reviewed. Applicant argues that the teachings are "anecdotal" and do not report a definitive scientific conclusion.

It is unclear to the Examiner how peer review would alter the teachings of the report that trials were stopped because they were failures? It is further unclear to the Examiner what Applicant's characterizing the teachings of the report as "anecdotal" is intended to mean. Is Applicant arguing that the trials were not actually stopped? Even Applicant admits that the trials reported in the *Marketletter* were stopped because "the statistical significance of the results did not warrant further spending on late clinical trials" which would seem to be scientific conclusion, i.e., the drug did not work. Also note that the report states that the drug first failed in phase II trials but was pushed into phase III trials regardless where it again failed to show "statistically significant results".

Applicant asserts that the Examiner is in error with respect to the Goodnow reference and that "the unpredictability described by Goodnow refers to the use and mechanism of action of corticosteroids". Applicant argues that the reference does not say that oral tolerance does not work and further argues that the reference states that clinical trials are underway. Applicant then dismisses the reference as mere opinion.

The reference states in the *Abstract*, "New experimental therapies aim to mimic tolerogenic antigen signals by chronically stimulating antigen receptors with antigens or antibodies to the receptor, or aim to block costimulatory pathways involving CD40 ligand, B7, or interleukin 2. Obtaining the desired response with these strategies is unpredictable because many of these signals have both tolerogenic and immunogenic roles." This "unpredictability does not appear to be referring to the "mechanism of action of corticosteroids" as Applicant asserts. Regarding the teaching that trials are underway, said teaching is noted. Also note, however, that the report does not indicate whether said trials are merely safety trials (phase I) or efficacy trials (phase II or III), thus nothing can be deduced from this teaching. And as set forth previously, the instant record contains no reports of success in oral tolerance trials, but it does contain reports of multiple failures in oral tolerance trials. Additionally, a complete reading of the reference would include a review of the teachings of the second column of page 2120 wherein the author further states that while mucosal tolerance has been achieved in experimental animals, "The first clinical trial of oral tolerance was unsuccessful, pointing to the need to understand better the mechanisms involved and to develop ways to achieve

more reliable linkage between tolerogenic antigen suitable tolerogenic costimuli". It is noted that no such attempt is made in the instant application. Finally note that while Applicant dismisses the opinion of the author, the American Association of Immunologists has recently named him a keynote speaker for the 2006 meeting of the AAI; the November/December 2005 AAI Newsletter states that Dr. Goodnow's work "has changed the conceptual framework of self-tolerance", indicating that his peers might value his opinion.

Applicant argues that WO 02/053092 demonstrates that oral tolerance can be accomplished.

Applicant's interpretation of the reference is noted. A complete reading of the reference, however, shows that numerous difficulties have been encountered in attempts to induce oral tolerance, difficulties not addressed in the instant application.

Applicant argues "The Examiner has discounted the evidence presented in the references by Husby et al. (1994) and McKown et al. (2000) that were provided by Dr. Jevnikar, which demonstrate the induction of tolerance in humans." Applicant reviews the findings of Moldoveanu et al., 2004.

Applicant appears to misunderstand the Examiner's position, the evidence has not been "discounted"; it is the Examiner's position that a more complete examination of the author's work serves to demonstrate unpredictability as set forth above, particularly in view of the fact that the claims recite essentially no limitations regarding the types of immune responses to be suppressed. Interestingly, Applicant submits that Moldoveanu (2004) teaches that "oral tolerance may not decrease "pre-existing" responses when this pre-existing immune response to KLH is overly robust", an embodiment that would be encompassed by the instant claims.

Applicant reviews the findings of McKown et al. (1999) and Carbone et al. (2004). Applicant argues that their findings do not indicate unpredictability and comprise only routine experimentation. Applicant argues that the authors were not employing methods of trial and error.

It remains the Examiner's position that the references teach what they teach - a complete lack of efficacy. Regarding whether or not the authors were employing methods of trial and error, there would seem to be two possibilities, first, that they were indeed employing trial and error. Applicant has rejected this possibility. A second likely possibility then would be that the authors were employing methods that, given their expertise in the field, were judged most likely to prove successful. There is no evidence that the authors were attempting to fail. As the methods did, however, fail, said failure would seem to be a demonstration of the unpredictability of inducing immune tolerance in humans.

Applicant argues that the Examiner has "discounted" the testimony of Inventor Jevnikar.

Applicant is advised that the Inventor's declaration has not been "discounted", indeed, it was thoroughly evaluated as set forth previously. However, in this instance the Inventor's opinion that his invention works has not been found to be persuasive, particularly in view of the evidence of record that it does not, for the reasons set forth here and previously.

Applicant argues "The Examiner's misapplication of the use of the term "unexpected" in Dr. Jevnikar's previous Declaration to support a basis of the rejection is an improper twisting of the inventor's meaning clearly contrary to what is true or was intended. It is inappropriate for the Examiner to remove the term "unexpected" from the context from which the term is used."

It is unclear how the Examiner has improperly twisted the term given that said term has not been used by the Examiner but rather was chosen by the Inventor, presumably in consultation with counsel.

Applicant argues "given the insight, guidance and examples provided by the disclosure of the present invention, the induction of tolerance in mammals in general and humans in particular is not so unpredictable as to render the claims of the application not enabled".

A review of the instant disclosure reveals that the eight examples deal exclusively with the production of the plants employed in the claimed method. It is unclear then how said examples could provide enablement for the claimed method.

Looking to the rest of the disclosure for insight and guidance, the entire teaching of the disclosure comprises no more regarding dosages and timing of administration, i.e., parameters critical to the actual methods that would be used to induce the tolerance, than do the claims themselves. Thus, it is unclear where the insight and guidance referred to by Applicant is to be found.

Applicant argues that "The enablement requirement does not require that every variation of a method produce optimal results. Applicants have provided references describing that oral tolerance can be achieved in mammals".

The Examiner does not disagree. The Examiner has, however, provided numerous references showing that major embodiments of the claimed invention have failed and would be expected to continue to fail even now, some 12+ years past the priority date of the instant application. Accordingly, the invention as broadly claimed stands rejected as being unpredictable and requiring of undue experimentation.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 52, 59-61, 63, 69-91, and 95 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/07581 (1992, IDS) in view of U.S. Patent No. 5,484,719 (IDS), for the reasons of record set forth in the action mailed 2/10/04 and maintained in the action mailed 10/08/04 and 4/18/05.

Applicant's arguments, filed 10/18/05, have been fully considered but they are not persuasive. Applicant argues a lack of motivation to combine the references.

As set forth previously, it is the Examiner's position that sound scientific reasoning would lead the ordinarily skilled artisan to the conclusion that if viral, bacterial, and fungal antigens could be efficiently produced in a plant, so could

tolerogenic antigens - there is no teaching of record that tolerogenic antigens differ from any other type of antigens. Antigens are routinely defined as substances capable of inducing an immune response. As set forth previously, WO 92/07581 teaches that tolerance as the induction of a suppressive immune response. Accordingly, this combined knowledge renders the inventions of the instant claims, i.e., compositions and methods for the induction of a suppressive immune responsive comprising administering antigens produced in plants orally, obvious.

7. No claim is allowed.

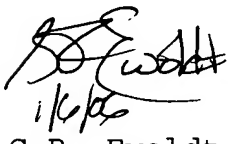
8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

10. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-

free). Additionally, the Technology Center receptionist can be reached at (571) 272-1600.



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